Remarks

This Amendment is responsive to the Final Office Action mailed June 22, 2010. Claims 1 and 3-15 are pending in the instant application, claims 13-15 have been withdrawn from consideration, and claim 2 has been previously canceled without prejudice or disclaimer. In the Action, the Office rejected claims 1 and 3-12.

Rejection – 35 U.S.C. § 103(a)

Claims 1 and 3-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nagashima *et al.* (Blood, **1998**, *91(10)*, 3850-3861) in view of Golay *et al.* (US 2007/0014785 A1). Applicant respectfully traverses the rejection.

Applicant respectfully submits that Nagashima *et al.* teaches the transfection of human NK cells (*i.e.*, NK-92 and YT2C2 cell lines) with retroviral vectors derived from MuLV. Notably, Nagashima fails to teach or suggest that transfection of $CD56^{dim}$ NK cells with a PINCO vector, or any vector derived from Epstein-Barr virus (EBV) is possible. The Office alleges that Golay teaches "the use of PINCO retroviral vector and Phoenix-Ampho cells for transfection with the exogenous gene," and that substituting "one known element (the PINCO expression vector and the Phoenix-Ampho cell line of Golay *et al.*) for another (MuLV and CRIP of Nagashima *et al.*) would have been obvious to one of ordinary skill in the art at the time of the invention."

Applicant respectfully submits that while Golay appears to teach the use of PINCO retroviral vector and Phoenix-Ampho cells, Golay further teaches that introduction of the exogenous gene is to T-lymphocytes, not NK cells or more precisely $CD56^{dim}$ NK cells. As a result, there appears to be no teaching, suggestion, or motivation for combining the teachings of Golay and Nagashima to achieve the features recited in Applicant's claims. As previously explained, while T-lymphocytes and NK cells are both lymphocytes, these cells are immunologically very different. T-lymphocytes mature in the thymus, play a central role in cell-mediated immunity, and are identified by the presence of T-cell antigen receptors (TCR) on the their surface. The surface immunochemistry (*e.g.*, TCR) of T-lymphocytes is responsible for the

adaptive immune response, hence the binding of the T-lymphocyte to the antigen of the major histocompatibility complexes (MHC-I) of other cells. In contrast, NK cells are not processed by the thymus, are cytotoxic lymphocytes that trigger an innate immune response, and NK cells lack T-cell antigen receptors. Natural killer cells induce apoptosis in cells that lack "self" markers (*i.e.*, major histocompatibility complexes). For at least these reasons, Applicant submits that one of ordinary skill in the art reading Nagashima and Golay either individually or together would not find the claimed inventions obvious.

Moreover, Applicant respectfully submits that the Office has failed to set forth a *prima facie* case of obviousness with respect to claim 5. In the previous Office Action mailed November 12, 2010, the Office rejected claim 5 under 35 U.S.C. § 102(b), and the present Office Action does not appear to address the features recited in claim 5 in making the obviousness rejection. As a result, the Office Action does not clearly articulate the alleged reasons why claim 5 would have been obvious to one of ordinary skill in the art. Applicant respectfully submits that for at least the above-mentioned reason, the claim rejection should be withdrawn.

Rejection – 35 U.S.C. § 103(a)

Claims 1 and 7-10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nagashima *et al.* (Blood, **1998**, *91(10)*, 3850-3861) in view of Fischer *et al.* (Exp. Clin. Cardiol. **2002**, *7(2/3)*, 106-112). Applicant respectfully traverses the rejection.

Applicant respectfully submits that the Office has failed to set forth a *prima facie* case of obviousness with respect to claims 1 and 7-10. In Applicant's previous response dated April 11, 2011, claim 1 was amended to recite that the packaging cell line to be transfected was a "**Phoenix cell line**." Nagashima teaches the use of a CRIP cell line, and Fischer does not appear to disclose the use of a Phoenix cell line. As a result, Nagashima and Fischer fail to teach or suggest *each and every claim feature*. For at least this reason, claims 1 and 7-10 cannot be considered obvious over Nagashima in view of Fischer.

Moreover, Applicant submits that Nagashima fails to teach the size of the transfected DNA or the maximum packaging capabilities of the CRIP cell line. Office asserts that Fischer

teaches "[t]hat inserts up to 6 to 7 Kb were known to be useable in retroviral vectors." Applicant submits that Fischer states "[B]y deleting these viral protein-coding regions from the genome, retroviruses are made replication defective and can offer a maximal packaging capability of 6 to 7 Kb (28)," which is dependent upon reference 28 (J. A. Levy, H. Fraenkel-Conrat, R. A. Owens; *Virology*, 3 Ed.: 1994, 129-133, 189-190) cited by Fischer. Upon careful examination of Levy, it is clear that the cited work covers the structure of retroviruses and components, and virus production (*i.e.,* the natural viral replication cycle, not engineered virus production). Levy, at no point in the text addresses deletion of viral protein-coding regions, replication deficiencies, or maximal packaging capabilities of retroviral vectors. Clearly, the claim made by Fischer with respect to maximal packaging capabilities of retroviral vectors (*e.g.*, 6 to 7 Kb) is not substantiated and therefore in light of Levy (the underlying reference) fails to serve as valid proof "[t]hat inserts up to 6 to 7 Kb were known to be useable in retroviral vectors." Applicant respectfully submits that for at least these reasons the claimed inventions are not obvious, and respectfully requests withdrawal of the rejection.

Rejection – 35 U.S.C. § 103(a)

Claims 11 and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nagashima *et al.* (Blood, **1998**, *91(10)*, 3850-3861) in view of Campana *et al.* (US 2005/0113564 A1). Applicant respectfully traverses the rejection.

Applicant respectfully submits that the present method is believed to be the first to result in the transfection of the $CD56^{dim}$ population: other methods, including that of Nagashima, are effective at transfecting the $CD56^{bright}$ population only. Therefore, a method capable of transfecting both $CD56^{bright}$ and **$CD56^{dim}$** NK cell population subsets, which possess immunologically distinct functions, would be highly advantageous. Transfection of the $CD56^{dim}$ population subset using a PINCO vector was found to be highly unexpected as prior art using either MuLV or MSCV were only capable of transfecting the $CD56^{bright}$ population as reported by Nagashima and Campana, respectively. Further, the unexpected transfection of the $CD56^{dim}$ population would not have been obvious to one of ordinary skill in the art and therefore one of ordinary skill in the art would not have found it obvious to label (*e.g.*, attach a GFP or CD8

marker) the population subset that at the instant of application had not been taught to be capable of transfection. Applicant respectfully submits that for at least these reasons the claimed inventions are not obvious, and respectfully requests withdrawal of the rejection.

In the event the Commissioner should decide that any additional fee or fee deficiency is due, the Commissioner is hereby authorized to charge any and all fees incurred as a result of entering or considering this document to deposit account number 03-0172.

Respectfully submitted,

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